Mixing Martinis

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monolayers approaching 100 nm in lateral dimension on the time scale of tens of microseconds. Lipid mixtures containing saturated and unsaturated lipids and cholesterol were studied under varying surface tension (0-40 mN/m) and temperature (270-323 K). Compositional lipid de-mixing and coexistence of liquid-expanded and liquid-condensed phases as well as liquid-ordered and liquid-disordered phases was reproduced. Formation of the more ordered phase induced by lowering the surface tension or temperature occurred via either nucleation and growth or spinodal decomposition. Using cluster analysis combined with Voronoi tessellation we characterized in detail the properties of the phases and kinetics of domain growth. Area fraction and lipid composition of each phase, and boundary length were obtained as a function of temperature and surface tension. We also simulated lipid monolayers connected to bilayer reservoirs in water, which are relevant for the function of lung surfactant. The distribution of phases between the monolayers and bilayers, and the effect of domains on monolayer stability were determined.

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Mixing Martinis: Atomistic Simulations of MscL in a Coarse Grained Environment

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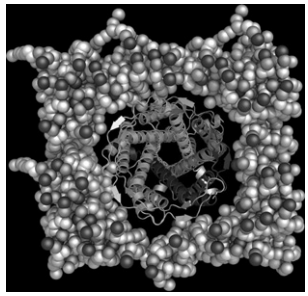
The large conductance mechanosensitive channel is a tension controlled safety valve in bacterial membranes, and is of interest for the development of controlled-release drug-delivery vesicles. Molecular dynamics simulations have been employed before to gain understanding in the mechanisms involved in opening the channel. In particular, atomistic simulations have been performed to assess the mechanistic details. Yet the time scales accessible in such simulations are too limited for observing opening. For that reason, coarse-grained simulations have been employed, which allow sampling larger systems for longer times. Yet such simulations fall short on the details of the mechanism. To combine the best of both worlds, a multiscale simulation setup has been developed in which MscL is included in atomistic detail. The surrounding membrane and solvent, which are of less interest, are modeled at the coarse grained level, using the MARTINI force field. The simulations add to building a comprehensive model of tension induced channel opening.



1217-Plat

Quantitative Membrane Bending Energies at Extreme Curvatures from Molecular Dynamics Simulations

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At mesoscopic length scales and small curvatures, Helfrich's well established continuum model [1] provides accurate membrane bending and stretching energies. For the small nanometer scales and extreme curvatures relevant for fundamental biological processes like synaptic fusion and tubulation, however, its validity is unclear. To test whether or not the bending energy remains a harmonic function of curvature, described by a simple bending modulus, we developed and applied a new type of collective umbrella sampling molecular dynamics (MD) simulations.

Most MD simulations computing bending moduli are limited to thermally accessible energies (a few kBT) and curvatures. In this limited regime, the harmonic approximation has been repeatedly confirmed. Very few simulation strategies exist to compute bending energies at higher curvatures, due to the inherent difficulty of controlling membrane structures. These simulation studies have generally verified the harmonic bending approximation but were limited by the requirements of a soft coarse grained lipid model[2], and unavoidable coupling between bending and stretching[3]. To overcome these limitations, we have developed a novel approach to control membrane curvature thereby accessing the regime of $<$10nm curvature radii and ~50 kBT energies. Our preliminary results show that at high curvatures, moduli have a small positive deviation from the harmonic approximation, that would not be discernible in the flat/thermal regime. As expected, we observe that increasing temperature decreases the elastic moduli and that ethanol and cholesterol act to soften and stiffen membranes, respectively.

[1] W. Helfrich, Naturforsch [C] 28, p693 (1973).
[2] V.A. Harmandris and M. Deserno, JCP 125, p204905 (2006).
[3] W.K. den Otter and W.J. Briels, JCP 118, p4712 (2003).

1218-Plat

Molecular Dynamics Simulations of Membrane Proteins: Getting the Details Right

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Over the past decade atomistic molecular dynamics simulations have become an established tool for studying the conformational dynamics and interactions with local environment of membrane proteins. While a great deal of valuable, molecular-level insight has been obtained from such simulations, in order to fully utilise their predictive power, it is important to continually validate and improve the methods and models that are used.

The accuracy of molecular dynamics simulations is dependent upon the quality of the force fields used to describe the interactions between particles in the system. Whilst numerous studies have compared different atomistic protein force fields, there have been fewer studies comparing force fields for membranes/membrane protein simulations. Thus it is timely to initiate such a study.

In the present work, we have tested the accuracy of five atomistic force fields used to simulate two different phospholipid membranes (namely the zwitterionic DPPC and POPC lipids). Multiple simulations, each 200 ns in length, have been performed to evaluate the reproduction of a range of physical properties. In addition, we have performed simulations of six different membrane proteins (3 alpha-helical and 3 beta-barrel proteins of varying size: melittin, KcsA, mitochondrial ADP/ATP carrier, OmpA, OmpG and FhuA) in both DPPC and POPC membranes using the same five lipid force fields, combined with appropriate protein force fields. Our simulations, which are in total over 60 microseconds in length, allow for a systematic comparison between frequently used combinations of lipid and protein force fields and thus will be a valuable resource for the membrane protein simulation community.

1219-Plat

Cholesterol Flip-Flop Dynamics in a Phospholipid Bilayer: All Atom Molecular Dynamics Simulations

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Presence of cholesterol (CHOL) molecules in cell membranes plays a key role in the structural properties of cell membranes. Also the dynamics of CHOL molecules in the cell membrane is an important biological process. Using all-atom molecular dynamics (MD) and parallel replica approach, we study the mechanism of CHOL flip-flop in a dipalmitoylphosphatidycholine (DPPC)-CHOL bilayer. The simulations are carried out at physiologically relevant CHOL concentration (30%), temperature 323 K and pressure 1 bar. The longest simulation is run for seven microseconds. CHOL flip-flop events are observed at a rate with a time constant in the submicrosecond regime. Figure 1 shows a CHOL flip-flop event. Once a flip-flop event is triggered, a CHOL molecule takes about 62 nanoseconds to migrate from one bilayer leaflet to the other. The energy barrier associated with these events is found to be 73 kJ/mol. Results for mechanical stresses in the bilayer will also be presented.

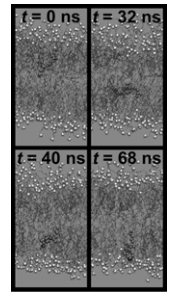

Fig. 1: Snapshots of CHOL flip-flop dynamics. The lipid head-groups, tail-groups and cholesterol molecules are shown in yellow, cyan and red, respectively. The flip-flopping molecule is highlighted with the hydroxyl head in blue and the rest in magenta.

1220-Plat

Computational Study of Self-Aggregation and Interaction of Amyloidgenic Peptide Oligomers with a Lipid Bilayer

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The toxicity of many neurodegenerative pathologies, including Alzheimer's, Parkinson's, and prion diseases, is thought to involve the interaction of oligomeric aggregates of amyloidogenic proteins with neuronal membranes. To gain insight into the molecular basis of toxicity, we conducted atomistic molecular dynamics simulations of prion and other amyloid-forming protein fragments in the presence of hydrated lipid bilayers. To probe peptide-bilayer interactions and peptide self-aggregation, we performed both canonical simulations and temperature virtual replica exchange (TVREX)[1] simulations totalling over 20 microseconds. In the canonical simulations, peptides rapidly partition at the water-bilayer interface but, due to the long conformational autocorrelation times of lipid bilayers, diffuse slowly and fail to aggregate within 2 microseconds. By contrast, TVREX enhances the rate of convergence of equilibrium